

L Number	Hits	Search Text	DB	Time stamp
1	2	CAR same steroid same receptor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/08/14 09:07
2	15	CAR same nuclear same receptor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/08/14 09:08
4	7	(CAR same nuclear same receptor) and choles\$7	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/08/14 09:13
5	8	phenobarb\$4 same choles\$7 same effect	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/08/14 09:14
-	5	constitutive same androstane same receptor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/08/14 09:01

	U	1	Document ID	Issue Date	Pages	Title
1	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 20010000472 A1	20010426	14	L-ergothioneine, milk thistle, and s-adenosylmethionine for the prevention, treatment and repair of
2	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 6103733 A	20000815	19	Method for increasing HDL cholesterol levels using heteroaromatic phenylmethanes
3	<input checked="" type="checkbox"/>	<input type="checkbox"/>	US 5908861 A	19990601	26	Methods for treating inflammation and inflammatory disease using pADPRT inhibitors
4	<input type="checkbox"/>	<input type="checkbox"/>	US 5006526 A	19910409	5	Method of treating a vertebrate animal to reduce plasma triglycerides and cholesterol levels and to alleviate and prevent atherosclerosis
5	<input type="checkbox"/>	<input type="checkbox"/>	US 4645774 A	19870224	8	Aminoethoxybenzylalcohol derivatives, process for their preparation and pharmaceutical compositions containing them
6	<input type="checkbox"/>	<input type="checkbox"/>	US 4605785 A	19860812	9	1,1-diphenylpropanol derivatives, process for their preparation and pharmaceutical compositions containing them
7	<input type="checkbox"/>	<input type="checkbox"/>	US 5006526 A	19910409	5	Treatment of atherosclerosis with ergot cpds. - reduces plasma cholesterol and tri:glyceride levels
8	<input type="checkbox"/>	<input type="checkbox"/>	EP 115205 A	19840808	8	Alpha-phenyl-alpha-ethyl-amino:ethoxy:benzyl alcohol cpds. - useful as stimulants of liver poly:substrate mono:oxygenase enzyme system

	Current OR	Current XRef	Retrieval Classif	Inventor	S	C	P	2
1	424/725	514/398; 514/46		Henderson, Todd R. et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	514/277	514/399; 514/400; 514/427; 544/333; 546/272.7; 546/343; 548/340.1; 548/346.1		Bachmann, Kenneth A. et al.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	514/456	514/309; 514/617; 514/619; 514/622; 514/825; 514/898		Kun, Ernestt	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	514/250	514/288; 514/824		Meier, Albert H. et al.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	514/317	514/428; 514/648; 546/241; 548/575; 564/324; 564/327		Toth, Edit et al.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6	568/649	558/389; 560/57; 562/468; 564/323; 564/326		Toth, Edit et al.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7				CINCOTTA, A H et al.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8				GOROG, S et al.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	3	4	5	Image Doc. Displayed	PT
1	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	US 20010000472	<input type="checkbox"/>
2	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	US 6103733	<input type="checkbox"/>
3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	US 5908861	<input type="checkbox"/>
4	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	US 5006526	<input type="checkbox"/>
5	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	US 4645774	<input type="checkbox"/>
6	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	US 4605785	<input type="checkbox"/>
7	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	US 5006526	<input type="checkbox"/>
8	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	US 4645774	<input type="checkbox"/>

09760367

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ZCAPLUS  
NEWS 7 Apr 22 BIOSIS Gene Names now available in TOXCENTER  
NEWS 8 Apr 22 Federal Research in Progress (FEDRIP) now available  
NEWS 9 Jun 03 New e-mail delivery for search results now available  
NEWS 10 Jun 10 MEDLINE Reload  
NEWS 11 Jun 10 PCTFULL has been reloaded  
NEWS 12 Jul 02 FOREGE no longer contains STANDARDS file segment  
NEWS 13 Jul 22 USAN to be reloaded July 28, 2002;  
saved answer sets no longer valid  
NEWS 14 Jul 29 Enhanced polymer searching in REGISTRY  
NEWS 15 Jul 30 NETFIRST to be removed from STN  
NEWS 16 Aug 08 CANCERLIT reload  
NEWS 17 Aug 08 PHARMAMarketLetter(PHARMAML) - new on STN  
NEWS 18 Aug 08 NTIS has been reloaded and enhanced  
NEWS 19 Aug 09 JAPIO to be reloaded August 18, 2002  
  
NEWS EXPRESS February 1 CURRENT WINDOWS VERSION IS V6.0d,  
CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),  
AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002  
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=> s cons? (p) androstane (p) receptor (p) choles?

3 FILES SEARCHED...

L1 15 CONS? (P) ANDROSTANE (P) RECEPTOR (P) CHOLES?

=> dup rem l1

PROCESSING COMPLETED FOR L1

L2 7 DUP REM L1 (8 DUPLICATES REMOVED)

=> d l2 total ibib kwic

L2 ANSWER 1 OF 7

MEDLINE

ACCESSION NUMBER: 2002418126 IN-PROCESS

DOCUMENT NUMBER: 22162479 PubMed ID: 12045201

TITLE: Cholesterol and Bile Acids Regulate Xenosensor Signaling  
in

Drug-mediated Induction of Cytochromes P450.

AUTHOR: Handschin Christoph; Podvinec Michael; Amherd Remo; Looser  
Renate; Ourlin Jean-Claude; Meyer Urs A

CORPORATE SOURCE: Division of Pharmacology/Neurobiology, Biozentrum of the  
University of Basel, Klingelbergstrasse 50-70, CH-4056  
Basel, Switzerland.

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Aug 16) 277 (33)  
29561-7.

Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals

ENTRY DATE: Entered STN: 20020813

Last Updated on STN: 20020813

AB Cytochromes P450 (CYP) **constitute** the major enzymatic system for  
metabolism of xenobiotics. Here we demonstrate that transcriptional  
activation of CYPs by the drug-sensing nuclear **receptors**  
pregnane X **receptor**, **constitutive androstane**  
**receptor**, and the chicken xenobiotic **receptor** (CXR) can  
be modulated by endogenous **cholesterol** and bile acids. Bile  
acids induce the chicken drug-activated CYP2H1 via CXR, whereas the  
hydroxylated metabolites of bile acids and oxysterols inhibit drug  
induction. The **cholesterol**-sensing liver X **receptor**  
competes with CXR, pregnane X **receptor**, or **constitutive**  
**androstane receptor** for regulation of drug-responsive

enhancers for chicken CYP2H1, human CYP3A4, or human CYP2B6, respectively. Thus, not only **cholesterol** 7 $\alpha$ -hydroxylase (CYP7A1), but also drug-inducible CYPs, are diametrically affected by these **receptors**. Our findings reveal new insights into the increasingly complex network of nuclear **receptors** regulating lipid homeostasis and drug metabolism.

L2 ANSWER 2 OF 7 MEDLINE DUPLICATE 1  
 ACCESSION NUMBER: 2002276876 MEDLINE  
 DOCUMENT NUMBER: 22012188 PubMed ID: 12016543  
 TITLE: Regulation of hepatic drug metabolism: role of the nuclear receptors PXR and CAR.  
 AUTHOR: Liddle Christopher; Goodwin Bryan  
 CORPORATE SOURCE: Department of Clinical Pharmacology and Storr Liver Unit, Westmead Millennium Institute, University of Sydney, Westmead Hospital, Westmead, Australia..  
 SOURCE: SEMINARS IN LIVER DISEASE, (2002) 22 (2) 115-22. Ref: 90  
 Journal code: 8110297. ISSN: 0272-8087.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 (REVIEW, TUTORIAL)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200207  
 ENTRY DATE: Entered STN: 20020518  
 Last Updated on STN: 20020709  
 Entered Medline: 20020708

AB Recent advances in the molecular biology of nuclear **receptors** have revealed that the pregnane X **receptor** (PXR) and the **constitutive androstane receptor** (CAR) are able to act as sensors for lipophilic xenobiotics, including therapeutic drugs. These **receptors** in turn regulate enzymes and transporters involved in drug metabolism and disposition in an adaptive fashion. An unexpected finding was that the PXR was able to recognize bile acids; transgenic animals lacking this **receptor** are at increased risk of bile acid-induced liver injury. These findings provide new insights into hepatic drug metabolism as well as mechanisms regulating **cholesterol** and bile acid homeostasis.

L2 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 2001:525915 CAPLUS  
 DOCUMENT NUMBER: 135:127155  
 TITLE: Screening constitutive androstane receptor (CAR) modulators for treatment of hypercholesterolemia associated diseases  
 INVENTOR(S): Lehmann, Jurgen M.; Shiau, Andrew Kwan-Nan  
 PATENT ASSIGNEE(S): Tularik Inc., USA  
 SOURCE: PCT Int. Appl., 75 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001051045	A2	20010719	WO 2001-US1111	20010112
WO 2001051045	A3	20011220		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, CM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
DE, ES, FI, FR, GB, GR, IE, IT, L, MC, NL, PT, SE, TR, BF,  
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-176398P P 20000113

AB This invention provides methods that are useful for identifying therapeutic agents for the treatment of a **constitutive androstane receptor** (CAR)-mediated disorder or condition. The methods include detg. whether the candidate therapeutic agent can: interact directly with CAR, modulate CAR-mediated gene expression, decrease CAR antagonist elevation of a **cholesterol** indicator in a mammal, or decrease a **cholesterol** level indicator in a mammal with a defective CAR. Also provided are CAR agonists. The invention also provides methods for producing a transgenic mouse having a genome with a disrupted CAR allele. The invention further provides methods for treating a CAR-mediated disorder or condition such as hypercholesterolemia, lipid disorders, atherosclerosis, and cardiovascular disorders.

IT mRNA

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(as a indicator for **cholesterol** level; screening  
**constitutive androstane receptor** (CAR)  
modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(high-d., as **cholesterol** indicator; screening  
**constitutive androstane receptor** (CAR)  
modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(low-d., as **cholesterol** indicator; screening  
**constitutive androstane receptor** (CAR)  
modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(very-low-d., as **cholesterol** indicator; screening  
**constitutive androstane receptor** (CAR)  
modulators for treatment of hypercholesterolemia assocd. diseases)

IT 57-88-5, **cholesterol**, biological studies

RL: BOC (Biological occurrence); BSU (Biological study, unclassified);  
BIOL (Biological study); OCCU (Occurrence)  
(serum; screening **constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

L2 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:817836 CAPLUS

DOCUMENT NUMBER: 136:112073

TITLE: Orphan nuclear receptors: the exotics of xenobiotics

AUTHOR(S): Xie, Wen; Evans, Ronald M.

CORPORATE SOURCE: Gene Expression Laboratory, The Salk Institute for  
Biological Studies, La Jolla, CA, 92037, USA

SOURCE: Journal of Biological Chemistry (2001), 276(41),  
37739-37742

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular  
Biology

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR  
THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

AB A review discusses the mol. complexity of xenobiotics and nuclear  
**receptor** (NR)-mediated xenobiotic regulation. Orphan NRs play a  
unique role in the regulation of cytochrome P 450 (CYP) genes by

functioning as atypical pleiotropic **receptors** for a remarkable diversity of xenobiotic compds. The identity of **constitutive androstane receptor** (CAR) as a xenobiotic **receptor** was first indicated by the ability of selective **androstane** metabolites to inhibit its **constitutive** activity. Similar to SXR (steroid and xenobiotic **receptor**) and its rodent ortholog PXR (pregnane X **receptor**), CAR also shows clear species-dependent ligand specificity. A combination of knockout and transgenic mouse studies revealed that activation of SXR/PXR is necessary and sufficient to both induce CYP3A enzymes and confer a resistance to toxic **cholestatic** bile acid lithocholic acid.

L2 ANSWER 5 OF 7 MEDLINE DUPLICATE 2  
 ACCESSION NUMBER: 2001514846 MEDLINE  
 DOCUMENT NUMBER: 21446829 PubMed ID: 11562429  
 TITLE: Multiple enhancer units mediate drug induction of CYP2H1  
 by

xenobiotic-sensing orphan nuclear receptor chicken  
 xenobiotic receptor.  
 AUTHOR: Handschin C; Podvinec M; Looser R; Amherd R; Meyer U A  
 CORPORATE SOURCE: Division of Pharmacology/Neurobiology, Biozentrum of the  
 University of Basel, Basel, Switzerland.  
 SOURCE: MOLECULAR PHARMACOLOGY, (2001 Oct) 60 (4) 681-9.  
 Journal code: 0035623. ISSN: 0026-895X.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200110  
 ENTRY DATE: Entered STN: 20010920  
 Last Updated on STN: 20011008  
 Entered Medline: 20011004

AB Binding of nuclear **receptors** to drug-responsive enhancer units  
 mediates transcriptional activation of cytochromes P-450 (P-450) by drugs  
 and xenobiotics. In previous studies, a 264-base-pair. . . to -1408  
 upstream of the chicken CYP2H1 transcriptional start-site increased gene  
 expression when activated by the chicken xenobiotic-sensing orphan  
 nuclear

**receptor** CXR. In extension of these studies, we now have  
 functionally analyzed a second distal drug-responsive element and  
 delimited a 643-. . . of the transcriptional start site of CYP2H1.

Both PBRUs were activated by CXR after treatment with different drugs. A  
 nuclear **receptor** binding site, a direct repeat-4 (DR-4) hexamer  
 repeat, was identified on the 240-bp PBRU. Site-directed mutagenesis of  
 this DR-4 abolished. . . the complex remained unaffected by unlabeled  
 240-bp PBRU with a mutated DR-4. In cross-species experiments, both the  
 human xenobiotic-sensing nuclear **receptors** pregnane X  
**receptor** and **constitutive androstane**  
**receptor** bound to this element, suggesting sequence  
**conservation** between chicken and mammalian PBRUs and between the  
 DNA binding domains of these **receptors**. Of two orphan nuclear  
**receptors** involved in **cholesterol** and bile acid  
 homeostasis, only chicken liver X **receptor** (LXR) but not chicken  
 farnesoid X **receptor** bound to the 240-bp PBRU. These results  
 suggest that CYP2H1 induction is explained by the combined effect of  
 multiple distal. . .

L2 ANSWER 6 OF 7 MEDLINE DUPLICATE 3  
 ACCESSION NUMBER: 2001078235 MEDLINE  
 DOCUMENT NUMBER: 20545466 PubMed ID: 10967108  
 TITLE: Topography of nicotinic acetylcholine receptor  
 membrane-embedded domains.  
 AUTHOR: Barrantes F J; Antollini S S; Blanton M P; Prieto M  
 CORPORATE SOURCE: Instituto de Investigaciones Bioquimicas de Bahia Blanca,

B8000FWB Bahia Blanca, Argentina.  
CONTRACT NUMBER: 1R03-TW01225-01 (FIC)  
R29NS35786 (NINDS)  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Dec 1) 275 (48)  
37333-9.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200101  
ENTRY DATE: Entered STN: 20010322  
Last Updated on STN: 20010322  
Entered Medline: 20010111

AB The topography of nicotinic acetylcholine **receptor** (AChR) membrane-embedded domains and the relative affinity of lipids for these protein regions were studied using fluorescence methods. Intact Torpedo. . . protein and transmembrane peptides were derivatized with N-(1-pyrenyl)maleimide (PM), purified, and reconstituted into asolectin liposomes. Fluorescence mapped to proteolytic fragments **consistent** with PM labeling of cysteine residues in alphaM1, alphaM4, gammaM1, and gammaM4. The topography of the pyrene-labeled Cys residues with. . . affinity for representative lipids were determined by differential fluorescence quenching with spin-labeled derivatives of fatty acids, phosphatidylcholine, and the steroids **cholestane** and **androstane**. Different spin label lipid analogs exhibit different selectivity for the whole AChR protein and its transmembrane domains. In all cases. . . of the presence of a substantial amount of non-helical structure, and/or of kinks attributable to the occurrence of the evolutionarily **conserved** proline residues. The latter is a striking feature of M1 in the AChR and all members of the rapid ligand-gated. . .

L2 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
ACCESSION NUMBER: 2000:526330 BIOSIS  
DOCUMENT NUMBER: PREV200000526330  
TITLE: Transcriptional control of hepatocanalicular transporter gene expression.  
AUTHOR(S): Muller, Michael (1)  
CORPORATE SOURCE: (1) Division of Gastroenterology and Hepatology, University  
Hospital Groningen, Hanzeplein 1, NL-9713GZ, Groningen Netherlands  
SOURCE: Seminars in Liver Disease, (2000) Vol. 20, No. 3, pp. 323-337. print.  
ISSN: 0272-8087.  
DOCUMENT TYPE: General Review  
LANGUAGE: English  
SUMMARY LANGUAGE: English

IT . . .  
Molecular Genetics (Biochemistry and Molecular Biophysics); Digestive System (Ingestion and Assimilation)

IT Chemicals & Biochemicals  
BSEP: bile salt transporter protein; **constitutive androstane receptor**; farnesoid X **receptors**:  
bile acid **receptor**; hepatocanalicular transport genes:  
transcriptional expression control; liver X **receptors**:  
dietary **cholesterol** sensors; multidrug resistance protein-1;  
multidrug resistance protein-2; multidrug resistance protein-3:  
basolateral anionic conjugate transporter, bile salt transporter;  
nuclear factor-kappa-B: stress response factor; nuclear  
ligand-activated **receptors**; p53: stress response factor;  
peroxisome proliferator activated **receptor**-alpha; pregnane X  
**receptor**: steroid binding activity, xenobiotic binding  
activity; sterol-responsive element binding proteins; transcription  
factors; mouse hepatic ABC transporter gene (Muridae): transcription

=> s cyp2b (p) cholesterol

L3 10 CYP2B (P) CHOLESTEROL

=> dup rem l3

PROCESSING COMPLETED FOR L3

L4 4 DUP REM L3 (6 DUPLICATES REMOVED)

=> d l4 total ibib kwic

L4 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:257045 CAPLUS

DOCUMENT NUMBER: 133:56561

TITLE: Differential suppression of liver-specific genes in regenerating rat liver induced by extended

hepatectomy

AUTHOR(S): Kurumiya, Yasuhiro; Nozawa, Katsura; Sakaguchi, Kenji;

CORPORATE SOURCE: Nagino, Masato; Nimura, Yuji; Yoshida, Shonen  
First Department of Surgery, Research Institute for Disease Mechanism and Control, Nagoya University School of Medicine, Nagoya, 466-8550, Japan

SOURCE: Journal of Hepatology (2000), 32(4), 636-644

CODEN: JOHEEC; ISSN: 0168-8278

PUBLISHER: Munksgaard International Publishers Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

ST serum albumin apolipoprotein phosphoenolpyruvate carboxykinase liver regeneration; PEPCK OTC **CYP2B** ODC gene hepatocyte proliferation; ornithine transcarbamylase cytochrome jun PCNA liver regeneration; HGF ornithine decarboxylase thymidine kinase hepatocyte proliferation; TK proliferating cell nuclear antigen DNA polymerase regeneration; actin GAPDH haptoglobin macroglobulin liver regeneration; blood **cholesterol** glucose bilirubin liver regeneration

L4 ANSWER 2 OF 4

MEDLINE

DUPLICATE 1

ACCESSION NUMBER: 2000004580 MEDLINE

DOCUMENT NUMBER: 20004580 PubMed ID: 10534307

TITLE: Effect of a ligand selective for peripheral benzodiazepine receptors on the expression of rat hepatic P-450 cytochromes: assessment of the effect in vivo and in a hepatocyte culture system.

AUTHOR: Yamada H; Matsuki Y; Yamaguchi T; Oguri K

CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan.

SOURCE: DRUG METABOLISM AND DISPOSITION, (1999 Nov) 27 (11) 1242-7.

Journal code: 9421550. ISSN: 0090-9556.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199911

ENTRY DATE: Entered STN: 20000111

Last Updated on STN: 20000111

Entered Medline: 19991124

AB The peripheral benzodiazepine receptor plays a role in the translocation

of **cholesterol** into mitochondria where steroidogenesis occurs. Sterols have been suggested to be involved in the regulation of the cytochrome P-450 (CYP)2B subfamily as the endogenous suppressor of this CYP. To investigate the role of **cholesterol** metabolites on the expression of CYPs, the effect of PK11195, a specific ligand of the peripheral benzodiazepine receptor and a stimulator of **cholesterol** transportation, on CYP expression was examined in rats in vivo and in cultured hepatocytes. As judged by the change in testosterone metabolic activity catalyzed by liver microsomes, i.p. injection of PK11195 into rats increased the **CYP2B** subfamily significantly. A trend in the induction of the CYP2A1, 2C11, and 3A isozymes was also observed. When PK11195 was . . . the magnitude of the effect was much greater than

that

observed in vivo. The inductive effect of PK11195 toward the **CYP2B** and 3A subfamilies was 2.3- and 6.5-fold greater, respectively, than that with phenobarbital. The inductive effect of PK11195 was confirmed. . . expression of these CYPs. This observation suggests that, if certain sterols play a role in the suppressive control of the **CYP2B** subfamily, they are produced in organelles other than the mitochondria.

L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:635125 CAPLUS

DOCUMENT NUMBER: 129:339755

TITLE: Regulation of rat hepatic cytochrome P450 expression by sterol biosynthesis inhibition: inhibitors of squalene synthase are potent inducers of CYP2B expression in primary cultured rat hepatocytes and

rat

liver

AUTHOR(S): Kocarek, Thomas A.; Kraniak, Janice M.; Reddy, Anita B.

CORPORATE SOURCE: Institute of Chemical Toxicology, Wayne State University, Detroit, MI, 48201, USA

SOURCE: Molecular Pharmacology (1998), 54(3), 474-484  
CODEN: MOPMA3; ISSN: 0026-895X

PUBLISHER: Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

IT 57-88-5, **Cholesterol**, biological studies 79-63-0, Lanosterol  
111-02-4, Squalene 9028-35-7, 3-Hydroxy-3-methylglutaryl CoA reductase  
96595-04-9, Pentoxifyresorufin O-dealkylase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(inhibitors of squalene synthase as inducers of **CYP2B**

expression in primary cultured rat hepatocytes and rat liver)

L4 ANSWER 4 OF 4

MEDLINE

DUPLICATE 2

ACCESSION NUMBER: 1998337723 MEDLINE

DOCUMENT NUMBER: 98337723 PubMed ID: 9674966

TITLE: Marked inhibition of hepatic cytochrome P450 activity in cholesterol-induced atherosclerosis in rabbits.

AUTHOR: Irizar A; Ioannides C

CORPORATE SOURCE: Molecular Toxicology Group, School of Biological Sciences, University of Surrey, Guildford, UK.

SOURCE: TOXICOLOGY, (1998 Apr 3) 126 (3) 179-93.  
Journal code: 0361055. ISSN: 0300-483X.

PUB. COUNTRY: Ireland

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199808

ENTRY DATE: Entered STN: 19980817

Last Updated on STN: 19980817

Entered Medline: 19980806

AB . . . and of other enzyme systems, in hepatic and extrahepatic tissues of rabbits rendered atherosclerotic by the dietary administration of 1%

**cholesterol** diets for 8 weeks. Individual cytochrome P450 proteins were monitored using diagnostic substrates and immunologically in Western blot analysis. The . . . determined immunologically, no major differences were evident between the control and the atherosclerotic rabbits. In vitro studies indicated that neither **cholesterol** nor palm oil inhibited cytochrome P450 activity. The effects of **cholesterol** treatment leading to atherosclerosis on kidney, heart and lung cytochrome P450 activities were isoform- and tissue-specific; no change was evident. . . in the heart activities, but in the lung and kidney cytochrome P450 activities were clearly modulated by the treatment with **cholesterol**. Apoprotein levels did not always parallel the changes in activities. Western blot analysis of aortic cytochromes P450 revealed that administration of **cholesterol**-rich diets enhanced CYP2B and CYP3A apoprotein levels. **Cholesterol** feeding to rabbits gave rise to a marked decrease in hepatic glutathione S-transferase activity but did not influence glutathione reductase. . . same treatment had no effect on catalase, glutathione peroxidase and superoxide dismutase. It is concluded that treatment of rabbits with **cholesterol**-rich diets leading to atherosclerosis gives rise to profound changes in the expression of cytochrome P450 proteins in the liver and. . .

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ZCAPLUS  
NEWS 7 Apr 22 BIOSIS Gene Names now available in TOXCENTER  
NEWS 8 Apr 22 Federal Research in Progress (FEDRIP) now available  
NEWS 9 Jun 03 New e-mail delivery for search results now available  
NEWS 10 Jun 10 MEDLINE Reload  
NEWS 11 Jun 10 PCTFULL has been reloaded  
NEWS 12 Jul 02 FOREGE no longer contains STANDARDS file segment  
NEWS 13 Jul 22 USAN to be reloaded July 28, 2002;  
saved answer sets no longer valid  
NEWS 14 Jul 29 Enhanced polymer searching in REGISTRY  
NEWS 15 Jul 30 NETFIRST to be removed from STN  
NEWS 16 Aug 08 CANCERLIT reload  
NEWS 17 Aug 08 PHARMAMarketLetter(PHARMAML) - new on STN  
NEWS 18 Aug 08 NTIS has been reloaded and enhanced  
NEWS 19 Aug 09 JAPIO to be reloaded August 18, 2002  
  
NEWS EXPRESS February 1 CURRENT WINDOWS VERSION IS V6.0d,  
CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),  
AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002  
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=> s constitutive (p) androstane (p) receptor

L1 219 CONSTITUTIVE (P) ANDROSTANE (P) RECEPTOR

=> s constitutive (p) androstane (p) receptor (p) screen?

L2 17 CONSTITUTIVE (P) ANDROSTANE (P) RECEPTOR (P) SCREEN?

=> s constitutive (p) androstane (p) receptor (p) screen? (p) compound

L3 4 CONSTITUTIVE (P) ANDROSTANE (P) RECEPTOR (P) SCREEN? (P)  
COMPOUN

D

=> s constitutive (p) androstane (p) receptor (p) assay (p) compound

L4 8 CONSTITUTIVE (P) ANDROSTANE (P) RECEPTOR (P) ASSAY (P) COMPOUND

=> s l2 and l3 and l4

L5 0 L2 AND L3 AND L4

=> s l2 or l3 or l4

L6 25 L2 OR L3 OR L4

=> dup rem l6

PROCESSING COMPLETED FOR L6

L7 10 DUP REM L6 (15 DUPLICATES REMOVED)

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L7 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2002:240977 CAPLUS

DOCUMENT NUMBER: 136:274330

TITLE: Sequence of a human cytochrome P450 3A7 gene promoter  
region and uses in drug screening

INVENTOR(S): Berkenstam, Anders; Bertilsson, Goeran; Blomquist,  
Patrik

PATENT ASSIGNEE(S): Biovitrum AB, Swed.

SOURCE: PCT Int. Appl., 39 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002024918	A1	20020328	WO 2001-SE2007	20010919

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CO,  
CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,  
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,  
LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PH, PL, PT, RO, RU, SD,  
SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU,  
ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

SE 2000-3393 A 20000922

REFERENCE COUNT:

3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

AB The present invention relates to an isolated human cytochrome P 450 3A7 (CYP3A7) promoter region, and identifies the pregnane activated **receptor** (PAR) responsive element in the CYP3A7 promoter region. The invention further discloses that **constitutive androstane receptor** (CAR) can upregulate the CYP3A7 promoter via xenobiotic response element (XREM). The invention also relates to **screening** methods for agents modulating the expression of CYP3A7, such agents being potentially useful in modulating metab. of endogenous and/or exogenous **compds.**, drug interaction, toxicity and/or bioavailability of drugs.

ST sequence human cytochrome P450 3A7 CYP3A7 promoter drug **screening**; gene CYP3A7 promoter pregnane activated **receptor** responsive element PAR; promoter CYP3A7 **constitutive androstane receptor** CAR regulation

IT Proteins  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (CAR (**constitutive androstane receptor**); sequence of a human cytochrome P 450 3A7 promoter region and uses in drug **screening**)

L7 ANSWER 2 OF 10 MEDLINE DUPLICATE 1  
ACCESSION NUMBER: 2002089312 MEDLINE  
DOCUMENT NUMBER: 21659720 PubMed ID: 11706036  
TITLE: Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor.  
AUTHOR: Kast Heidi R; Goodwin Bryan; Tarr Paul T; Jones Stacey A; Anisfeld Andrew M; Stoltz Catherine M; Tontoz Peter; Klier Steve; Willson Timothy M; Edwards Peter A  
CORPORATE SOURCE: Department of Biological Chemistry and Medicine, UCLA, Los Angeles, California 90095, USA.  
CONTRACT NUMBER: HL30568 (NHLBI)  
HL68445 (NHLBI)  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Jan 25) 277 (4) 2908-15.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200202  
ENTRY DATE: Entered STN: 20020131  
Last Updated on STN: 20020226

Entered Medline: 20020225

AB The multidrug resistance-associated protein 2 (MRP2, ABCC2), mediates the efflux of several conjugated **compounds** across the apical membrane of the hepatocyte into the bile canaliculi. We identified MRP2 in

a **screen** designed to isolate genes that are regulated by the farnesoid X-activated **receptor** (FXR, NR1H4). MRP2 mRNA levels were induced following treatment of human or rat hepatocytes with either naturally occurring (chenodeoxycholic acid) or synthetic (GW4064) FXR ligands. In addition, we have shown that MRP2 expression is regulated by the pregnane X **receptor** (PXR, NR1I2) and **constitutive androstane receptor** (CAR, NR1I3). Thus, treatment of rodent hepatocytes with PXR or CAR agonists results in a robust induction of MRP2 mRNA. . . . 8 nucleotides (ER-8). PXR, CAR, and FXR bound with high affinity to this element as heterodimers with the retinoid X **receptor** alpha (RXRalpha, NR2B1). Luciferase reporter gene constructs containing 1 kb of the rat MRP2 promoter were prepared and transiently transfected. . . . conferring PXR, CAR, and FXR responsiveness on a heterologous thymidine kinase promoter. Mutation of the ER-8 element abolished the nuclear **receptor** response. These studies demonstrate that MRP2 is regulated by three distinct nuclear **receptor** signaling pathways that converge on a common response element in the 5'-flanking region of this gene.

L7 ANSWER 3 OF 10 MEDLINE DUPLICATE 2  
ACCESSION NUMBER: 2002374737 MEDLINE  
DOCUMENT NUMBER: 22116398 PubMed ID: 12120277  
TITLE: PXR, CAR and drug metabolism.  
AUTHOR: Willson Timothy M; Kliever Steven A  
CORPORATE SOURCE: GlaxoSmithKline, 5 Moore Drive, Research Triangle Park, North Carolina 27709, USA.. tmw20653@gsk.com  
SOURCE: Nat Rev Drug Discov, (2002 Apr) 1 (4) 259-66. Ref: 103  
Journal code: 101124171.  
PUB. COUNTRY: England: United Kingdom  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
General Review; (REVIEW)  
(REVIEW, TUTORIAL)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200207  
ENTRY DATE: Entered STN: 20020718  
Last Updated on STN: 20020731  
Entered Medline: 20020730

AB . . . harmful chemicals are also involved in drug metabolism, and can cause adverse drug-drug interactions. Two closely related orphan nuclear hormone **receptors**--the pregnane X **receptor** (PXR) and the **constitutive androstane receptor** (CAR)--have recently emerged as transcriptional regulators of cytochrome P450 expression that couple xenobiotic exposure to oxidative metabolism. In this review, . . . examination of the roles of PXR and CAR as xenobiotic sensors, and discuss the application of this knowledge to toxicological **screening** in drug discovery.

L7 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2002 ACS  
ACCESSION NUMBER: 2001:713686 CAPLUS  
DOCUMENT NUMBER: 135:267693  
TITLE: **Constitutive androstane receptor** ligand **screening** using method involving clotrimazole  
INVENTOR(S): Collins, Jon L.; Parks, Derek J.  
PATENT ASSIGNEE(S): Glaxo Group Limited, UK  
SOURCE: PCT Int. Appl., 26 pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1

## PATENT INFORMATION

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001071361	A2	20010927	WO 2001-US9233	20010322
WO 2001071361	A3	20020606		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2001055815 A1 20011227 US 2001-814569 20010322

PRIORITY APPLN. INFO.: US 2000-191493P P 20000323

TI **Constitutive androstane receptor** ligand  
**screening** using method involving clotrimazole

ST **constitutive androstane receptor** ligand  
**screening** clotrimazole; human sequence **constitutive androstane receptor** LBD fragment

IT Androgen **receptors**  
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(CAR (**constitutive androstane receptor**);  
**constitutive androstane receptor** ligand  
**screening** using method involving clotrimazole)

IT Spheres  
(beads, solid support; **constitutive androstane receptor** ligand **screening** using method involving clotrimazole and CAR ligand binding domain-contg. polypeptide attached to bead solid support)

IT Drug delivery systems  
Drug **screening**  
Protein sequences  
(**constitutive androstane receptor** ligand  
**screening** using method involving clotrimazole)

IT Biotinylation  
(**constitutive androstane receptor** ligand  
**screening** using method involving clotrimazole and CAR ligand binding domain-contg. polypeptide attached to coated bead solid support)

IT Fusion proteins (chimeric proteins)  
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(**constitutive androstane receptor** ligand-binding domain; **constitutive androstane receptor** ligand **screening** using method involving clotrimazole)

IT Protein motifs  
(ligand-binding domain of **constitutive androstane receptor**; **constitutive androstane receptor** ligand **screening** using method involving clotrimazole)

IT Avidins  
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)  
(solid support bead coating; **constitutive androstane receptor** ligand **screening** using method involving clotrimazole and CAR ligand binding domain-contg. polypeptide attached to coated bead solid support)

IT 363631-04-3  
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)  
(amino acid sequence; **constitutive androstane receptor** ligand **screening** using method involving clotrimazole)

IT 23593-75-1, Clotrimazole 23593-75-1D, Clotrimazole, radiolabeled  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (constitutive androstane receptor ligand  
 screening using method involving clotrimazole)  
 IT 58-85-5, Biotin 9013-20-1, Streptavidin  
 RL: BUU (Biological use, unclassified); BIOL (Biological study); USES  
 (Uses)  
 (solid support bead coating; constitutive androstane  
 receptor ligand screening using method involving  
 clotrimazole and CAR ligand binding domain-contg. polypeptide attached  
 to coated bead solid support)  
 IT 363593-56-0 364059-93-8  
 RL: PRP (Properties)  
 (unclaimed sequence; constitutive androstane  
 receptor ligand screening using method involving  
 clotrimazole)

L7 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:525915 CAPLUS

DOCUMENT NUMBER: 135:127155

TITLE: Screening constitutive  
 androstane receptor (CAR) modulators  
 for treatment of hypercholesterolemia associated  
 diseases

INVENTOR(S): Lehmann, Jurgen M.; Shiau, Andrew Kwan-Nan

PATENT ASSIGNEE(S): Tularik Inc., USA

SOURCE: PCT Int. Appl., 75 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001051045	A2	20010719	WO 2001-US1111	20010112
WO 2001051045	A3	20011220		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,  
 CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
 HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,  
 LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,  
 SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,  
 YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
 DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-176398P P 20000113

TI Screening constitutive androstane  
 receptor (CAR) modulators for treatment of hypercholesterolemia  
 associated diseases

ST constitutive androstane receptor CAR  
 modulator screening hypercholesterolemia

IT Transcriptional regulation  
 (CAR-mediated; screening constitutive  
 androstane receptor (CAR) modulators for treatment of  
 hypercholesterolemia assocd. diseases)

IT Genetic element  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (CAR-responsive, DR-4 or DR-5; screening constitutive  
 androstane receptor (CAR) modulators for treatment of  
 hypercholesterolemia assocd. diseases)

IT Gene, animal  
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL  
 (Biological study)  
 (CAR.beta.; screening constitutive  
 androstane receptor (CAR) modulators for treatment of

hypercholesterolemia assocd. diseases)

IT Estrogen **receptors**  
 Glucocorticoid **receptors**  
 Mineralocorticoid **receptors**  
 Progesterone **receptors**  
 Retinoid **receptors**  
 Thyroid hormone **receptors**  
 Vitamin D **receptors**  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (DNA-binding domain from; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Transcription factors  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (GAL4, DNA-binding domain from; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Transcription factors  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (SRC-1 (steroid **receptor** coactivator-1), **receptor** binding domain of; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Antiarteriosclerotics  
 (antiatherosclerotics; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT mRNA  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (as a indicator for cholesterol level; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipids, biological studies  
 RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)  
 (blood; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Androgen **receptors**  
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (**constitutive**, CAR.alpha. or CAR.beta.; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Mutation  
 (deletion, of CAR; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Resonance fluorescence  
 (energy transfer; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Fluorescent indicators  
 Isotope indicators  
 (for labeling CAR ligands; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Proteins, specific or class  
 RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)  
 (green fluorescent, gene for, as reporter; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (high-d., as cholesterol indicator; **screening constitutive androstane receptor** (CAR)

modulators for treatment of hypercholesterolemia assocd. diseases)

IT Mutation  
(insertion, of CAR; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Peptides, biological studies  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (labeled; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (low-d., as cholesterol indicator; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipids, biological studies  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (metabolic disorders, treatment of; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Fluorometry  
(polarization; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Cardiovascular agents  
Drug **screening**  
Molecular cloning  
(**screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Reporter gene  
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)  
(**screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Peptides, biological studies  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (sensor; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Mammal (Mammalia)  
Mouse  
(transgenic, CAE allele-disrupted; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Hypercholesterolemia  
(treatment of; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (very-low-d., as cholesterol indicator; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 198705-46-3 301654-35-3 338961-03-8 351153-65-6 351153-66-7  
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
(CAR agonist; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 1153-51-1, 5.alpha.-androst-16-en-3.alpha.-ol 7657-50-3 95118-94-8, 5.alpha.-Androst-16-en-3.alpha.-ol acetate  
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(CAR ligand; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 225916-35-8  
 RL: BAC (Biological activity or effector, except adverse); BPR  
 (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
 (amino acid sequence; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 9001-78-9, Alkaline phosphatase 9014-00-0, luciferase 9031-11-2, .beta.-Galactosidase 9040-07-7, Chloramphenicol acetyltransferase  
 RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)  
 (gene for, as reporter; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 81-88-9  
 RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)  
 (labeled peptide; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 76150-91-9, 1,4-Bis[2-(3,5-dichloropyridyloxy)]benzene)  
 RL: BAC (Biological activity or effector, except adverse); BPR  
 (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
 (ligand for CAR; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 128-23-4, 5.beta.-pregnan-3,20 dione  
 RL: BAC (Biological activity or effector, except adverse); BPR  
 (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)  
 (ligand for CAR.alpha.; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 1404-04-2, neomycin  
 RL: BSU (Biological study, unclassified); BIOL (Biological study)  
 (resistance gene as marker gene; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 57-88-5, cholesterol, biological studies  
 RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)  
 (serum; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 351237-24-6, 4: PN: WO0151045 SEQID: 4 unclaimed DNA 351237-25-7, 5:  
 PN: WO0151045 SEQID: 5 unclaimed DNA 351237-26-8, 6: PN: WO0151045 SEQID: 6 unclaimed DNA 351237-27-9, 8: PN: WO0151045 SEQID: 8 unclaimed DNA 351237-29-1 351237-30-4  
 RL: PRP (Properties)  
 (unclaimed nucleotide sequence; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

IT 197731-92-3 351237-22-4 351237-23-5 351237-28-0  
 RL: PRP (Properties)  
 (unclaimed protein sequence; **screening constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

ACCESSION NUMBER: 2001:168249 CAPLUS  
 DOCUMENT NUMBER: 134:217982  
 TITLE: Chromatin-based RAR/RXR heterodimer-regulated transcription system and its use in screening for transcription modulators  
 INVENTOR(S): Chambon, Pierre; Dilworth, F. Jeffrey; Fromental-Ramain, Catherine  
 PATENT ASSIGNEE(S): Institut National de la Sante et de la Recherche Medicale, Fr.; Centre National de la Recherche Scientifique; Universite Louis Pasteur; Bristol-Myers Squibb Company  
 SOURCE: PCT Int. Appl., 51 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001016597	A1	20010308	WO 1999-US20018	19990901
W: AU, CA, IL, JP, MX, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

IT **Receptors**

RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)  
 (CAR (**constitutive androstane receptors**);  
 chromatin-based RAR/RXR heterodimer-regulated transcription system and its use in **screening** for transcription modulators)

ACCESSION NUMBER: 2001475469 MEDLINE  
 DOCUMENT NUMBER: 21410114 PubMed ID: 11518807  
 TITLE: Conservation of signaling pathways of xenobiotic-sensing orphan nuclear receptors, chicken xenobiotic receptor, constitutive androstane receptor, and pregnane X receptor, from birds to humans.  
 AUTHOR: Handschin C; Podvinec M; Stockli J; Hoffmann K; Meyer U A  
 CORPORATE SOURCE: Division of Pharmacology/Neurobiology, Biozentrum of the University of Basel, CH-4056 Basel, Switzerland.  
 SOURCE: MOLECULAR ENDOCRINOLOGY, (2001 Sep) 15 (9) 1571-85.  
 Journal code: 8801431. ISSN: 0888-8809.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200201  
 ENTRY DATE: Entered STN: 20010827  
 Last Updated on STN: 20020125  
 Entered Medline: 20020114

AB Chicken xenobiotic **receptor**, pregnane X **receptor**, and **constitutive androstane receptor** are orphan nuclear **receptors** that have recently been discovered to regulate drug- and steroid-mediated induction of hepatic cytochromes P450 (CYP). This induction is part. . . experiments in the chicken hepatoma cell line LMH that suggest evolutionary conservation of the signaling pathways triggered by pregnane X **receptor**, **constitutive androstane receptor**, and chicken xenobiotic **receptor**. Thus, the phenobarbital-inducible enhancer units of the mouse Cyp2b10, rat CYP2B2, and human CYP2B6 genes were activated in reporter gene **assays** by the same **compounds** that activate the chicken CYP2H1 phenobarbital-inducible enhancer units.

Chicken xenobiotic **receptor**, pregnane X **receptor**, and **constitutive androstane receptor** all bound to the CYP2H1 phenobarbital-inducible enhancer units in gel-shift experiments. In CV-1 cell transactivation **assays**, mammalian pregnane X **receptors** activate the chicken phenobarbital-inducible enhancer units to the same extent as does chicken xenobiotic **receptor**, each **receptor** maintaining its species-specific ligand spectrum. To assess the reported role of protein phosphorylation in drug-mediated induction, we treated LMH cells. . . comparable to those seen on CYP2Bs and CYP3As in mammalian primary hepatocyte cultures. These results indicate that closely related nuclear **receptors**, transcription factors, and signaling pathways are mediating the transcriptional activation of multiple genes by xenobiotics in chicken, rodents, and man.

L7 ANSWER 8 OF 10 MEDLINE DUPLICATE 4  
 ACCESSION NUMBER: 2000270219 MEDLINE  
 DOCUMENT NUMBER: 20270219 PubMed ID: 10748001  
 TITLE: Orphan nuclear receptors constitutive androstane receptor and pregnane X receptor share xenobiotic and steroid ligands.  
 AUTHOR: Moore L B; Parks D J; Jones S A; Bledsoe R K; Consler T G; Stimmel J B; Goodwin B; Liddle C; Blanchard S G; Willson T M; Collins J L; Kliewer S A  
 CORPORATE SOURCE: Department of Molecular Endocrinology, Glaxo Wellcome Research and Development, Research Triangle Park, North Carolina 27709, USA.  
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 May 19) 275 (20) 15122-7.  
 Journal code: 2985121R. ISSN: 0021-9258.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200006  
 ENTRY DATE: Entered STN: 20000629  
 Last Updated on STN: 20000629  
 Entered Medline: 20000621  
 AB Xenobiotics induce the transcription of cytochromes P450 (CYPs) 2B and 3A through the **constitutive androstane receptor** (CAR; NR1I3) and pregnane X **receptor** (PXR; NR1I2), respectively. In this report, we have systematically compared a series of xenobiotics and natural steroids for their effects. . . on mouse and human CAR and PXR. Our results demonstrate dual regulation of PXR and CAR by a subset of **compounds** that affect CYP expression. Moreover, there are marked pharmacological differences between the mouse (m) and human (h) orthologs of both. . . PXR. Similarly, the PXR activator clotrimazole is a potent deactivator of hCAR. Using radioligand binding and fluorescence resonance energy transfer **assays**, we demonstrate that several of the **compounds** that regulate mouse and human CAR, including natural steroids, bind directly to the **receptors**. Our results suggest that CAR, like PXR, is a steroid **receptor** that is capable of recognizing structurally diverse **compounds**. Moreover, our findings underscore the complexity in the physiologic response to xenobiotics.

L7 ANSWER 9 OF 10 MEDLINE DUPLICATE 5  
 ACCESSION NUMBER: 2001305626 MEDLINE  
 DOCUMENT NUMBER: 20525078 PubMed ID: 11075820  
 TITLE: Estrogen activation of the nuclear orphan receptor CAR (constitutive active receptor) in induction of the mouse Cyp2b10 gene.  
 AUTHOR: Kawamoto T; Kakizaki S; Yoshinari K; Negishi M

CORPORATE SOURCE: Pharmacogenetics Section, Laboratory of Reproductive and Developmental Toxicology, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina 27709, USA.

SOURCE: MOLECULAR ENDOCRINOLOGY, (2000 Nov) 14 (11) 1897-905.  
Journal code: 8801431. ISSN: 0888-8809.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200105  
ENTRY DATE: Entered STN: 20010604  
Last Updated on STN: 20010604  
Entered Medline: 20010531

AB The nuclear orphan **receptor** CAR (constitutively active **receptor** or **constitutive androstane receptor**) can be activated in response to xenochemical exposure, such as activation by phenobarbital of a response element called NR1 found

in the CYP2B gene. Here various steroids were **screened** for potential endogenous chemicals that may activate CAR, using the NR1 enhancer and Cyp2b10 induction in transfected HepG2 cell and/or. . .

is an effective activator of CAR in both female and male mice, suggesting a biological and/or toxicological role of this **receptor** in estrogen metabolism. In addition to mouse CAR, estrogens activated rat CAR, whereas human CAR did not respond well to. . .

L7 ANSWER 10 OF 10 MEDLINE DUPLICATE 6

ACCESSION NUMBER: 1998322543 MEDLINE  
DOCUMENT NUMBER: 98322543 PubMed ID: 9658407  
TITLE: Molecular cloning of xSRC-3, a novel transcription coactivator from Xenopus, that is related to AIB1, p/CIP, and TIF2.  
AUTHOR: Kim H J; Lee S K; Na S Y; Choi H S; Lee J W  
CORPORATE SOURCE: College of Pharmacy, Chonnam National University, Kwangju, South Korea.  
SOURCE: MOLECULAR ENDOCRINOLOGY, (1998 Jul) 12 (7) 1038-47.  
Journal code: 8801431. ISSN: 0888-8809.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199810  
ENTRY DATE: Entered STN: 19981020  
Last Updated on STN: 19981020  
Entered Medline: 19981005

AB Nuclear **receptors** regulate transcription by binding to specific DNA response elements of target genes. Herein, we report the molecular cloning and characterization of a novel Xenopus cDNA encoding a transcription coactivator xSRC-3 by using retinoid X **receptor** (RXR) as a bait in the yeast two-hybrid **screening**. It belongs to a growing coactivator family that includes a steroid **receptor** coactivator amplified in breast cancer (AIB1), p300/ CREB-binding protein (CBP)-interacting protein (p/ CIP), and transcriptional intermediate factor 2 (TIF2). It also interacts with a series of nuclear **receptors** including retinoic acid **receptor** (RAR), thyroid hormone **receptor** (TR), and orphan nuclear **receptors** [hepatocyte nuclear **receptor** 4 (HNF4) and **constitutive androstane receptor** (CAR)]. However, it does not interact with small heterodimer partner (SHP), an orphan nuclear **receptor** known to antagonize ligand-dependent transactivation of other nuclear **receptors**. In CV-1 cells, cotransfection of xSRC-3 differentially stimulates ligand-induced transactivation of RXR, TR, and RAR in a dose-dependent manner.

Interestingly . . . and early stages of oocyte development, suggesting that studies xSRC-3 may lead to better understanding of the roles nuclear **receptors** play in oocyte development as well as liver-specific gene expression.

=> log y

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
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FULL ESTIMATED COST	0.21	0.21

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=> s cons? (p) androstane (p) receptor (p) choles?

3 FILES SEARCHED...

L1 15 CONS? (P) ANDROSTANE (P) RECEPTOR (P) CHOLES?

=> dup rem l1

PROCESSING COMPLETED FOR L1

L2 7 DUP REM L1 (8 DUPLICATES REMOVED)

=> d l2 total ibib kwic

L2 ANSWER 1 OF 7 MEDLINE  
ACCESSION NUMBER: 2002418126 IN-PROCESS  
DOCUMENT NUMBER: 22162479 PubMed ID: 12045201  
TITLE: Cholesterol and Bile Acids Regulate Xenosensor Signaling in Drug-mediated Induction of Cytochromes P450.  
AUTHOR: Handschin Christoph; Podvinec Michael; Amherd Remo; Looser Renate; Ourlin Jean-Claude; Meyer Urs A  
CORPORATE SOURCE: Division of Pharmacology/Neurobiology, Biozentrum of the University of Basel, Klingelbergstrasse 50-70, CH-4056 Basel, Switzerland.  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Aug 16) 277 (33) 29561-7.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals  
ENTRY DATE: Entered STN: 20020813  
Last Updated on STN: 20020813

AB Cytochromes P450 (CYP) **constitute** the major enzymatic system for metabolism of xenobiotics. Here we demonstrate that transcriptional activation of CYPs by the drug-sensing nuclear **receptors** pregnane X **receptor**, **constitutive androstane receptor**, and the chicken xenobiotic **receptor** (CXR) can be modulated by endogenous **cholesterol** and bile acids. Bile acids induce the chicken drug-activated CYP2H1 via CXR, whereas the hydroxylated metabolites of bile acids and oxysterols inhibit drug induction. The **cholesterol**-sensing liver X **receptor** competes with CXR, pregnane X **receptor**, or **constitutive androstane receptor** for regulation of drug-responsive

enhancers from chicken CYP2H1, human CYP3A4, or human CYP2B6, respectively. Thus, not only **cholesterol** 7alpha-hydroxylase (CYP7A1), but also drug-inducible CYPs, are diametrically affected by these **receptors**. Our findings reveal new insights into the increasingly complex network of nuclear **receptors** regulating lipid homeostasis and drug metabolism.

L2 ANSWER 2 OF 7 MEDLINE DUPLICATE 1  
 ACCESSION NUMBER: 2002276876 MEDLINE  
 DOCUMENT NUMBER: 22012188 PubMed ID: 12016543  
 TITLE: Regulation of hepatic drug metabolism: role of the nuclear receptors PXR and CAR.  
 AUTHOR: Liddle Christopher; Goodwin Bryan  
 CORPORATE SOURCE: Department of Clinical Pharmacology and Storr Liver Unit, Westmead Millennium Institute, University of Sydney, Westmead Hospital, Westmead, Australia..  
 chris.liddle@wmi.usyd.edu.au  
 SOURCE: SEMINARS IN LIVER DISEASE, (2002) 22 (2) 115-22. Ref: 90  
 Journal code: 8110297. ISSN: 0272-8087.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200207  
 ENTRY DATE: Entered STN: 20020518  
 Last Updated on STN: 20020709  
 Entered Medline: 20020708

AB Recent advances in the molecular biology of nuclear **receptors** have revealed that the pregnane X **receptor** (PXR) and the **constitutive androstane receptor** (CAR) are able to act as sensors for lipophilic xenobiotics, including therapeutic drugs. These **receptors** in turn regulate enzymes and transporters involved in drug metabolism and disposition in an adaptive fashion. An unexpected finding was that the PXR was able to recognize bile acids; transgenic animals lacking this **receptor** are at increased risk of bile acid-induced liver injury. These findings provide new insights into hepatic drug metabolism as well as mechanisms regulating **cholesterol** and bile acid homeostasis.

L2 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2002 ACS  
 ACCESSION NUMBER: 2001:525915 CAPLUS  
 DOCUMENT NUMBER: 135:127155  
 TITLE: Screening constitutive androstane receptor (CAR) modulators for treatment of hypercholesterolemia associated diseases  
 INVENTOR(S): Lehmann, Jurgen M.; Shiau, Andrew Kwan-Nan  
 PATENT ASSIGNEE(S): Tularik Inc., USA  
 SOURCE: PCT Int. Appl., 75 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001051045	A2	20010719	WO 2001-US1111	20010112
WO 2001051045	A3	20011220		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,

YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,  
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,  
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-176398P P 20000113

AB This invention provides methods that are useful for identifying therapeutic agents for the treatment of a **constitutive androstane receptor** (CAR)-mediated disorder or condition. The methods include detg. whether the candidate therapeutic agent can: interact directly with CAR, modulate CAR-mediated gene expression, decrease CAR antagonist elevation of a **cholesterol** indicator in a mammal, or decrease a **cholesterol** level indicator in a mammal with a defective CAR. Also provided are CAR agonists. The invention also provides methods for producing a transgenic mouse having a genome with a disrupted CAR allele. The invention further provides methods for treating a CAR-mediated disorder or condition such as hypercholesterolemia, lipid disorders, atherosclerosis, and cardiovascular disorders.

IT mRNA

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(as an indicator for **cholesterol** level; screening  
**constitutive androstane receptor** (CAR)  
modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(high-d., as **cholesterol** indicator; screening  
**constitutive androstane receptor** (CAR)  
modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(low-d., as **cholesterol** indicator; screening  
**constitutive androstane receptor** (CAR)  
modulators for treatment of hypercholesterolemia assocd. diseases)

IT Lipoproteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(very-low-d., as **cholesterol** indicator; screening  
**constitutive androstane receptor** (CAR)  
modulators for treatment of hypercholesterolemia assocd. diseases)

IT 57-88-5, **cholesterol**, biological studies

RL: BOC (Biological occurrence); BSU (Biological study, unclassified);  
BIOL (Biological study); OCCU (Occurrence)  
(serum; screening **constitutive androstane receptor** (CAR) modulators for treatment of hypercholesterolemia assocd. diseases)

L2 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:817836 CAPLUS

DOCUMENT NUMBER: 136:112073

TITLE: Orphan nuclear receptors: the exotics of xenobiotics

AUTHOR(S): Xie, Wen; Evans, Ronald M.

CORPORATE SOURCE: Gene Expression Laboratory, The Salk Institute for  
Biological Studies, La Jolla, CA, 92037, USA

SOURCE: Journal of Biological Chemistry (2001), 276(41),  
37739-37742

CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular  
Biology

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS  
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review discusses the mol. complexity of xenobiotics and nuclear  
**receptor** (NR)-mediated xenobiotic regulation. Orphan NRs play a  
unique role in the regulation of cytochrome P 450 (CYP) genes by  
functioning as atypical pleiotropic **receptors** for a remarkable

diversity of xenobiotic compds. The identity of **constitutive androstane receptor** (CAR) as a xenobiotic **receptor** was first indicated by the ability of selective **androstane** metabolites to inhibit its **constitutive** activity. Similar to SXR (steroid and xenobiotic **receptor**) and its rodent ortholog PXR (pregnane X **receptor**), CAR also shows clear species-dependent ligand specificity. A combination of knockout and transgenic mouse studies revealed that activation of SXR/PXR is necessary and sufficient to both induce CYP3A enzymes and confer a resistance to toxic **cholestatic** bile acid lithocholic acid.

L2 ANSWER 5 OF 7 MEDLINE DUPLICATE 2  
 ACCESSION NUMBER: 2001514846 MEDLINE  
 DOCUMENT NUMBER: 21446829 PubMed ID: 11562429  
 TITLE: Multiple enhancer units mediate drug induction of CYP2H1 by xenobiotic-sensing orphan nuclear receptor chicken xenobiotic receptor.  
 AUTHOR: Handschin C; Podvinec M; Looser R; Amherd R; Meyer U A  
 CORPORATE SOURCE: Division of Pharmacology/Neurobiology, Biozentrum of the University of Basel, Basel, Switzerland.  
 SOURCE: MOLECULAR PHARMACOLOGY, (2001 Oct) 60 (4) 681-9.  
 Journal code: 0035623. ISSN: 0026-895X.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200110  
 ENTRY DATE: Entered STN: 20010920  
 Last Updated on STN: 20011008  
 Entered Medline: 20011004

AB Binding of nuclear **receptors** to drug-responsive enhancer units mediates transcriptional activation of cytochromes P-450 (P-450) by drugs and xenobiotics. In previous studies, a 264-base-pair. . . to -1408 upstream of the chicken CYP2H1 transcriptional start-site increased gene expression when activated by the chicken xenobiotic-sensing orphan nuclear **receptor** CXR. In extension of these studies, we now have functionally analyzed a second distal drug-responsive element and delimited a 643-. . . of the transcriptional start site of CYP2H1. Both PBRUs were activated by CXR after treatment with different drugs. A nuclear **receptor** binding site, a direct repeat-4 (DR-4) hexamer repeat, was identified on the 240-bp PBRU. Site-directed mutagenesis of this DR-4 abolished. . . the complex remained unaffected by unlabeled 240-bp PBRU with a mutated DR-4. In cross-species experiments, both the human xenobiotic-sensing nuclear **receptors** pregnane X **receptor** and **constitutive androstane receptor** bound to this element, suggesting sequence **conservation** between chicken and mammalian PBRUs and between the DNA binding domains of these **receptors**. Of two orphan nuclear **receptors** involved in **cholesterol** and bile acid homeostasis, only chicken liver X **receptor** (LXR) but not chicken farnesoid X **receptor** bound to the 240-bp PBRU. These results suggest that CYP2H1 induction is explained by the combined effect of multiple distal. . .

L2 ANSWER 6 OF 7 MEDLINE DUPLICATE 3  
 ACCESSION NUMBER: 2001078235 MEDLINE  
 DOCUMENT NUMBER: 20545466 PubMed ID: 10967108  
 TITLE: Topography of nicotinic acetylcholine receptor membrane-embedded domains.  
 AUTHOR: Barrantes F J; Antollini S S; Blanton M P; Prieto M  
 CORPORATE SOURCE: Instituto de Investigaciones Bioquimicas de Bahia Blanca, B8000FWB Bahia Blanca, Argentina.  
 CONTRACT NUMBER: 1R03-TW01225-01 (FIC)  
 R29NS35786 (NINDS)  
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Dec 1) 275 (48)

37333-9.

Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200101  
ENTRY DATE: Entered STN: 20010322  
Last Updated on STN: 20010322  
Entered Medline: 20010111

AB The topography of nicotinic acetylcholine **receptor** (AChR) membrane-embedded domains and the relative affinity of lipids for these protein regions were studied using fluorescence methods. Intact Torpedo. . . protein and transmembrane peptides were derivatized with N-(1-pyrenyl)maleimide (PM), purified, and reconstituted into asolectin liposomes. Fluorescence mapped to proteolytic fragments **consistent** with PM labeling of cysteine residues in alphaM1, alphaM4, gammaM1, and gammaM4. The topography of the pyrene-labeled Cys residues with. . . affinity for representative lipids were determined by differential fluorescence quenching with spin-labeled derivatives of fatty acids, phosphatidylcholine, and the steroids **cholestane** and **androstandane**. Different spin label lipid analogs exhibit different selectivity for the whole AChR protein and its transmembrane domains. In all cases. . . of the presence of a substantial amount of non-helical structure, and/or of kinks attributable to the occurrence of the evolutionarily **conserved** proline residues. The latter is a striking feature of M1 in the AChR and all members of the rapid ligand-gated. . .

L2 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.  
ACCESSION NUMBER: 2000:526330 BIOSIS  
DOCUMENT NUMBER: PREV200000526330  
TITLE: Transcriptional control of hepatocanalicular transporter gene expression.  
AUTHOR(S): Muller, Michael (1)  
CORPORATE SOURCE: (1) Division of Gastroenterology and Hepatology, University Hospital Groningen, Hanzeplein 1, NL-9713GZ, Groningen Netherlands  
SOURCE: Seminars in Liver Disease, (2000) Vol. 20, No. 3, pp. 323-337. print.  
ISSN: 0272-8087.  
DOCUMENT TYPE: General Review  
LANGUAGE: English  
SUMMARY LANGUAGE: English

IT . . .  
Molecular Genetics (Biochemistry and Molecular Biophysics); Digestive System (Ingestion and Assimilation)

IT Chemicals & Biochemicals  
BSEP: bile salt transporter protein; **constitutive androstandane receptor**; farnesoid X **receptors**: bile acid **receptor**; hepatocanalicular transport genes: transcriptional expression control; liver X **receptors**: dietary **cholesterol** sensors; multidrug resistance protein-1; multidrug resistance protein-2; multidrug resistance protein-3: basolateral anionic conjugate transporter, bile salt transporter; nuclear factor-kappa-B: stress response factor; nuclear ligand-activated **receptors**; p53: stress response factor; peroxisome proliferator activated **receptor**-alpha; pregnane X **receptor**: steroid binding activity, xenobiotic binding activity; sterol-responsive element binding proteins; transcription factors; mouse hepatic ABC transporter gene (Muridae): transcription regulation

=> s cyp2b (p) cholesterol

L3 10 CYP2B (P) CHOLESTEROL

=> dup rem l3

PROCESSING COMPLETED FOR L3

L4 4 DUP REM L3 (6 DUPLICATES REMOVED)

=> d l4 total ibib kwic

L4 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2000:257045 CAPLUS

DOCUMENT NUMBER: 133:56561

TITLE: Differential suppression of liver-specific genes in regenerating rat liver induced by extended hepatectomy

AUTHOR(S): Kurumiya, Yasuhiro; Nozawa, Katsura; Sakaguchi, Kenji; Nagino, Masato; Nimura, Yuji; Yoshida, Shonen

CORPORATE SOURCE: First Department of Surgery, Research Institute for Disease Mechanism and Control, Nagoya University School of Medicine, Nagoya, 466-8550, Japan

SOURCE: Journal of Hepatology (2000), 32(4), 636-644  
CODEN: JOHEEC; ISSN: 0168-8278

PUBLISHER: Munksgaard International Publishers Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ST serum albumin apolipoprotein phosphoenolpyruvate carboxykinase liver regeneration; PEPCK OTC **CYP2B** ODC gene hepatocyte proliferation; ornithine transcarbamylase cytochrome jun PCNA liver regeneration; HGF ornithine decarboxylase thymidine kinase hepatocyte proliferation; TK proliferating cell nuclear antigen DNA polymerase regeneration; actin GAPDH haptoglobin macroglobulin liver regeneration; blood **cholesterol** glucose bilirubin liver regeneration

L4 ANSWER 2 OF 4 MEDLINE

DUPLICATE 1

ACCESSION NUMBER: 2000004580 MEDLINE

DOCUMENT NUMBER: 20004580 PubMed ID: 10534307

TITLE: Effect of a ligand selective for peripheral benzodiazepine receptors on the expression of rat hepatic P-450 cytochromes: assessment of the effect in vivo and in a hepatocyte culture system.

AUTHOR: Yamada H; Matsuki Y; Yamaguchi T; Oguri K

CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan.

SOURCE: DRUG METABOLISM AND DISPOSITION, (1999 Nov) 27 (11) 1242-7.  
Journal code: 9421550. ISSN: 0090-9556.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199911

ENTRY DATE: Entered STN: 20000111

Last Updated on STN: 20000111

Entered Medline: 19991124

AB The peripheral benzodiazepine receptor plays a role in the translocation of **cholesterol** into mitochondria where steroidogenesis occurs. Sterols have been suggested to be involved in the regulation of the cytochrome P-450 (CYP)2B subfamily as the endogenous suppressor of this CYP. To investigate the role of **cholesterol** metabolites on the expression of CYPs, the effect of PK11195, a specific ligand of the peripheral benzodiazepine receptor and a stimulator of **cholesterol** transportation, on CYP expression was examined in rats in vivo and in cultured hepatocytes. As judged by the change in testosterone metabolic

activity catalyzed by liver microsomes, i.p. injection of PK11195 into rats increased the **CYP2B** subfamily significantly. A trend in the induction of the CYP2A1, 2C11, and 3A isozymes was also observed. When PK11195 was . . . the magnitude of the effect was much greater than that observed in vivo. The inductive effect of PK11195 toward the **CYP2B** and 3A subfamilies was 2.3- and 6.5-fold greater, respectively, than that with phenobarbital. The inductive effect of PK11195 was confirmed. . . expression of these CYPs. This observation suggests that, if certain sterols play a role in the suppressive control of the **CYP2B** subfamily, they are produced in organelles other than the mitochondria.

L4 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1998:635125 CAPLUS  
DOCUMENT NUMBER: 129:339755  
TITLE: Regulation of rat hepatic cytochrome P450 expression by sterol biosynthesis inhibition: inhibitors of squalene synthase are potent inducers of CYP2B expression in primary cultured rat hepatocytes and rat liver  
AUTHOR(S): Kocarek, Thomas A.; Kraniak, Janice M.; Reddy, Anita B.  
CORPORATE SOURCE: Institute of Chemical Toxicology, Wayne State University, Detroit, MI, 48201, USA  
SOURCE: Molecular Pharmacology (1998), 54(3), 474-484  
CODEN: MOPMA3; ISSN: 0026-895X  
PUBLISHER: Williams & Wilkins  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
IT 57-88-5, **Cholesterol**, biological studies 79-63-0, Lanosterol 111-02-4, Squalene 9028-35-7, 3-Hydroxy-3-methylglutaryl CoA reductase 96595-04-9, Pentoxifyresorufin O-dealkylase  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(inhibitors of squalene synthase as inducers of **CYP2B** expression in primary cultured rat hepatocytes and rat liver)

L4 ANSWER 4 OF 4 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 1998337723 MEDLINE  
DOCUMENT NUMBER: 98337723 PubMed ID: 9674966  
TITLE: Marked inhibition of hepatic cytochrome P450 activity in cholesterol-induced atherosclerosis in rabbits.  
AUTHOR: Irizar A; Ioannides C  
CORPORATE SOURCE: Molecular Toxicology Group, School of Biological Sciences, University of Surrey, Guildford, UK.  
SOURCE: TOXICOLOGY, (1998 Apr 3) 126 (3) 179-93.  
Journal code: 0361055. ISSN: 0300-483X.  
PUB. COUNTRY: Ireland  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199808  
ENTRY DATE: Entered STN: 19980817  
Last Updated on STN: 19980817  
Entered Medline: 19980806

AB . . . and of other enzyme systems, in hepatic and extrahepatic tissues of rabbits rendered atherosclerotic by the dietary administration of 1% **cholesterol** diets for 8 weeks. Individual cytochrome P450 proteins were monitored using diagnostic substrates and immunologically in Western blot analysis. The . . . determined immunologically, no major differences were evident between the control and the atherosclerotic rabbits. In vitro studies indicated that neither **cholesterol** nor palm oil inhibited cytochrome P450 activity. The effects of **cholesterol** treatment leading to atherosclerosis on kidney, heart and lung cytochrome P450 activities were isoform- and tissue-specific; no change was evident. . . in the heart activities, but in the lung and

kidney cytochrome P450 activities were clearly modulated by the treatment with **cholesterol**. Apoprotein levels did not always parallel the changes in activities. Western blot analysis of aortic cytochromes P450 revealed that administration of **cholesterol**-rich diets enhanced **CYP2B** and **CYP3A** apoprotein levels. **Cholesterol** feeding to rabbits gave rise to a marked decrease in hepatic glutathione S-transferase activity but did not influence glutathione reductase. . . . same treatment had no effect on catalase, glutathione peroxidase and superoxide dismutase. It is concluded that treatment of rabbits with **cholesterol**-rich diets leading to atherosclerosis gives rise to profound changes in the expression of cytochrome P450 proteins in the liver and. . . .

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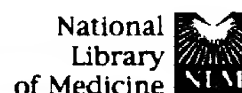
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Drug Metab Dispos. 2002 Feb;30(2):208-11.

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Mol Cell Biol. 1998 Oct;18(10):5652-8.

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Changes in serum lipids and lipoproteins in epileptic children treated with anticonvulsants.  
J Paediatr Child Health. 1997 Jun;33(3):242-5.

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Franzoni E, Govoni M, D'Addato S, Gualandi S, Sangiorgi Z, Descovich GC, Salvioli GP.  
Total cholesterol, high-density lipoprotein cholesterol, and triglycerides in children receiving antiepileptic drugs.  
Epilepsia. 1992 Sep-Oct;33(5):932-5.

Thanks a lot...

Joseph F. Murphy, Ph.D.  
Patent Examiner, Art Unit 1646  
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CM1 9A01  
Mailbox: 10C01  
(703) 305-7245

# Effects of long-term treatment with antiepileptic drugs on serum lipid levels in children with epilepsy

J.M. Eiris, MD; S. Lojo, PhD; M.C. Del Río, PhD; I. Novo, MD;  
M. Bravo, MD; P. Pavón, MD; and M. Castro-Gago, MD

**Article abstract**—We determined serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), and triglycerides (TGs) in 125 healthy children and in 119 children with epilepsy who had been receiving carbamazepine (58 children), phenobarbital (22 children), or valproic acid (39 children) for 7 months to 10.5 years (mean, 5.8 years). None of the variables considered was significantly correlated with time elapsed since start of treatment or with drug concentration in serum. In the groups receiving carbamazepine or phenobarbital, mean TC, HDL-C, and LDL-C levels were higher than in the control group, the differences being statistically significant for all except LDL-C in the phenobarbital group. In neither group did mean TC/HDL-C ratio or mean LDL-C/HDL-C ratio differ significantly from the corresponding control-group mean. In the group receiving valproic acid, mean TC level, mean LDL-C level, mean TC/HDL-C ratio, and mean LDL-C/HDL-C ratio were significantly lower than in the control group. In none of the treated groups did mean VLDL-C or TG level differ significantly from the corresponding control-group mean. Our results suggest, in contrast to previous reports, that the effects on the serum lipid profile of long-term treatment with hepatic-enzyme-inducing antiepileptic drugs (such as carbamazepine and phenobarbital) are probably not beneficial as regards risk of atherosclerosis-related disease. Our results additionally suggest a need for careful monitoring of serum cholesterol levels in children with epilepsy receiving carbamazepine or phenobarbital.

NEUROLOGY 1995;45:1155-1157

Childhood epilepsy often requires prolonged treatment with antiepileptic drugs (AEDs), in some cases continuing throughout the patient's life. Epidemiologic studies have indicated that mortality due to atherosclerosis-related heart disease is lower in treated epileptics than in the general population.<sup>1,2</sup> A number of authors have reported that treatment with hepatic-enzyme-inducing AEDs—such as carbamazepine, phenobarbital, and phenytoin—leads to increased high-density lipoprotein cholesterol (HDL-C) levels in serum.<sup>3-9</sup> Since the risk of coronary heart disease is positively correlated with high serum levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) and negatively correlated with high serum levels of HDL-C and with a high ratio of serum HDL-C to serum LDL-C,<sup>10-12</sup> Muuronen et al<sup>1</sup> suggested that the lower mortality due to coronary atherosclerosis in the epileptic population may reflect increases in HDL-C levels in response to treatment with hepatic-enzyme-inducing AEDs.

Some authors have reported that hepatic-enzyme-inducing AEDs cause not only long-term in-

creases in serum HDL-C levels but also short-term increases (over the first year of treatment) in serum levels of TC, LDL-C, and triglycerides (TGs).<sup>13,14</sup> Other studies have suggested that treatment with carbamazepine leads to long-term increases in all cholesterol fractions,<sup>15</sup> or that short-term treatment with hepatic-enzyme-inducing AEDs leads to increases in the levels of TC but not of HDL-C.<sup>16</sup> The literature on the effects of hepatic-enzyme-inducing AEDs on serum lipid profiles (and, by extension, on risk of atherosclerosis) is thus contradictory: it is, for example, entirely unclear whether epileptic children receiving hepatic-enzyme-inducing AEDs should follow a low-fat diet, as recommended by Franzoni et al.<sup>16</sup>

In the published studies on the effect of hepatic-enzyme-inducing AEDs on serum lipid profiles, the samples have mostly comprised adults<sup>3,4,6,13,14,17,18</sup> or adults and children together<sup>7,19</sup>; in only a few studies have the samples been of children alone.<sup>15,16,20</sup> In the work reported here, we investigated serum levels of cholesterol, cholesterol fractions, and TGs in 119 children with epilepsy who had been receiving

From the Department of Pediatrics (Drs. Eiris, Novo, Bravo, Pavón, and Castro-Gago), Division of Pediatric Neurology, and the Central Laboratory Service (Drs. Lojo and Del Río), Hospital General de Galicia, Clínico Universitario, Santiago de Compostela, Spain.

Received April 11, 1994. Accepted in final form November 28, 1994.

Address correspondence and reprint requests to Dr. M. Castro-Gago, Department of Pediatrics, Division of Pediatric Neurology, Hospital General de Galicia, 15705 Santiago de Compostela, Spain.

June 1995 NEUROLOGY 45 1155

Table. Basic statistics and results in each of the four groups

	Control	Carbamazepine	Phenobarbital	Valproic acid
Number of subjects, M/F	64/61	37/21	10/12	23/16
Age (yr), M/F	10.6 (2.8)/10.4 (2.9)	11.8 (2.4)/11.3 (2.7)	9.5 (3.1)/7.5 (2.5)	10.4 (2.6)/10.2 (3.3)
Duration of therapy (yr), M/F		3.7 (2.1)/3.8 (2.6)	6.2 (3.1)/5.1 (1.6)	3.3 (1.6)/3.9 (2.2)
Drug concentration in serum (μg/ml), M/F		5.5 (1.2)/6.3 (1.3)	14.3 (4.8)/12.9 (4.9)	62.2 (21.2)/57.1 (19.1)
TC (mg/dl)	172.20 (25.0)	193.56 (31.6)*	190.50 (34.5)*	153.82 (20.9)†
TGs (mg/dl)	65 (21)	69 (25)	61 (21)	58 (21)
HDL-C (mg/dl)	55.50 (13.4)	64.15 (18.1)†	63.35 (20.6)*	55.40 (15.5)
LDL-C (mg/dl)	103.80 (21.6)	114.40 (30.9)*	113.36 (32.4)	85.20 (18.0)†
VLDL-C (mg/dl)	13.8 (7.7)	13.7 (5.4)	13.6 (6.0)	11.8 (4.1)
TC/HDL-C ratio	3.26 (0.84)	3.17 (0.90)	3.18 (0.82)	2.88 (0.68)*
LDL-C/HDL-C ratio	2.01 (0.75)	1.91 (0.83)	1.91 (0.82)	1.64 (0.84)*

Numbers in parentheses are standard deviations.

\*  $p < 0.05$ . HDL-C High-density lipoprotein cholesterol.  
†  $p < 0.001$ . LDL-C Low-density lipoprotein cholesterol.  
TC Total cholesterol. VLDL-C Very low-density lipoprotein cholesterol.  
TGs Triglycerides.

carbamazepine, phenobarbital, or valproic acid over a long period (mean, 5.8 years) and in 125 healthy children from the same region (Galicia, northwest Spain) and with similar diet.

**Methods.** Basic statistics for the four groups of subjects (carbamazepine, phenobarbital, valproic acid, and control) are listed in the table. Blood samples were taken between 8:30 and 9:30 AM after an overnight fast and stored at  $-40^{\circ}\text{C}$  until analysis. TGs and TC were determined by colorimetry with a Hitachi 747 automated analyzer (Boehringer Mannheim Diagnostics). The various cholesterol fractions were determined with a Rep Ultra-30 system (Helena Laboratories), which is based on electrophoretic separation and subsequent enzymatic quantification of cholesterol and cholesterol esters associated with each lipoprotein fraction. Student's  $t$  test and linear regression analysis were employed to assess the significance of the results.

**Results.** In the epileptic group, there was no significant correlation between serum lipid levels and age, sex, time elapsed since start of treatment, drug dosage, or drug concentration in serum. Similarly, in the control group there was no significant correlation between serum lipid levels and age or sex. Mean serum TC levels were significantly higher in the groups receiving carbamazepine ( $194 \pm 32$  mg/dl) or phenobarbital ( $191 \pm 35$  mg/dl) than in the control group ( $172 \pm 25$  mg/dl); mean serum TC level in the group receiving valproic acid ( $154 \pm 21$  mg/dl), on the other hand, was significantly lower than in the control group (table). Serum TC level exceeded 200 mg/dl in 41% of the subjects receiving carbamazepine and 50% of the subjects receiving phenobarbital, but in only 12% of control-group subjects; by contrast, TC level did not exceed 200 mg/dl in any of the subjects receiving valproic acid. Mean HDL-C levels were significantly higher in the groups receiving carbamazepine ( $64 \pm 18$  mg/dl) or phenobarbital ( $63 \pm 21$  mg/dl) than in the

control group ( $56 \pm 13$  mg/dl); however, mean HDL-C level in the group receiving valproic acid ( $55 \pm 16$  mg/dl) did not differ significantly from that in the control group (table). Mean LDL-C level was significantly higher in the group receiving carbamazepine ( $114 \pm 31$  mg/dl) and nonsignificantly higher in the group receiving phenobarbital ( $113 \pm 32$  mg/dl) than in the control group ( $104 \pm 22$  mg/dl); mean LDL-C level in the group receiving valproic acid ( $85 \pm 18$  mg/dl) was significantly lower than in the control group (table). There were no significant differences in mean TG level or mean very low-density lipoprotein cholesterol level (table) between the control group and any of the treated groups. Mean LDL-C/HDL-C ratio was significantly lower in the group receiving valproic acid ( $1.64 \pm 0.84$ ) than in the control group ( $2.01 \pm 0.75$ ), but did not differ significantly from the control group in the other two treated groups (table). Likewise, mean TC/HDL-C ratio was significantly lower in the group receiving valproic acid ( $2.88 \pm 0.68$ ) than in the control group ( $3.26 \pm 0.84$ ) and again did not differ significantly from the control group in the other two treated groups (table).

**Discussion.** Our sample consisted of 119 children with epilepsy who were taking AEDs for 7 months to 10.5 years; only four patients—two in the carbamazepine group and two in the valproic acid group—were treated for less than 1 year. In all cases, the treatment was appropriate for the control of epilepsy (mean time elapsed since last attack:  $61 \pm 34$  months) and serum levels of the drug were within the corresponding therapeutic range. Mean TC, HDL-C, and LDL-C levels were all higher in the carbamazepine- and phenobarbital-treated groups than in the control group (the differences being statistically significant except for LDL-C in the phenobarbital group), although in neither case did mean LDL-C/HDL-C ratio or mean

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TC/HDL-C ratio differ significantly from the corresponding control-group mean.

Excepting LDL-C and TC in the phenobarbital group, our results constitute statistically significant confirmation of the findings of Heldenberg et al<sup>15</sup> and are in contrast to reports that TC and LDL-C levels are high only during the initial period of treatment.<sup>9,14,17</sup> Equally, our results do not support the assertion that TC levels rise as a result of increased LDL-C levels only,<sup>16</sup> but suggest that the increase in TC is due to both LDL-C and HDL-C.

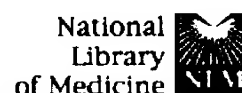
In the group treated with valproic acid (which does not induce hepatic enzymes), mean TC and LDL-C levels, mean LDL-C/HDL-C ratio, and mean TC/HDL-C ratio were significantly lower than in the control group. This is in accordance with previous studies,<sup>15,16,19</sup> although in one study<sup>20</sup> there were no significant differences between treated and control groups.

The Committee on Nutrition of the American Academy of Pediatrics (AAP) has classified serum TC levels in the range of 170 to 199 mg/dl as "borderline" and levels in excess of 200 mg/dl as "high."<sup>21</sup> We found that serum TC level exceeded 200 mg/dl in 41% of carbamazepine-treated children and in 50% of phenobarbital-treated children (as opposed to 12% of control-group children). This suggests a need for careful monitoring of serum lipid levels in children with epilepsy receiving these drugs. The AAP statement<sup>21</sup> points out that TC is an imperfect predictor of the risk of coronary vascular disease; thus, in children with high TC levels, LDL-C levels should also be determined. LDL-C levels in the range of 110 to 129 mg/dl are defined by the AAP as "borderline," while levels in excess of 129 mg/dl are defined as "high." In our study, LDL-C level exceeded 129 mg/dl in 29% of carbamazepine-treated children and 23% of phenobarbital-treated children (as opposed to only 9% of control-group children), but in only one valproic acid-treated child was LDL-C level high.

The normal ranges for serum cholesterol and its fractions are wide and appear to be dependent upon sex and age. The effects of hepatic-enzyme-inducing AEDs on serum lipid profile (and thus on risk of atherosclerosis) seem to be accurately evaluated only with reference to pretreatment levels in specific patients. Long-term prospective studies are required to clarify the effects of hepatic-enzyme-inducing AEDs on lipid metabolism in children. Despite the need for longer-term research, the results of the present study clearly indicate that serum lipid profiles should be carefully monitored in children receiving carbamazepine or phenobarbital. If analysis reveals high TC or LDL-C levels in serum, a low-fat diet<sup>21</sup> may be indicated. Serum lipid levels in children receiving valproic acid do not require special attention.

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## Changes in serum lipids and lipoproteins in epileptic children treated with anticonvulsants.

Verrotti A, Domizio S, Angelozzi B, Sabatino G, Morgese G, Chiarelli F.

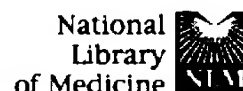
Department of Pediatrics, University of Chieti, Italy.

**OBJECTIVE:** To assess the effect of long-term treatment of phenobarbital, carbamazepine and sodium valproate on serum lipids and lipoproteins in epileptic children. **METHODOLOGY:** One hundred and fourteen (55 male, 59 female) children and adolescents suffering from various types of epilepsy who received different antiepileptic drugs were studied. The patients were subdivided into three groups according to their therapy: (i) carbamazepine (35 patients); (ii) phenobarbital (34 patients); and (iii) sodium valproate (45 patients). One-hundred healthy sex- and age-matched children served as controls. Lipids and lipoprotein profile were evaluated before the beginning of the anticonvulsant therapy and after at least 2.5 years. In the patients receiving phenobarbital, we re-evaluated 12 children (seven male, five female) at the end of therapy. **RESULTS:** The children receiving phenobarbital showed high levels of serum total cholesterol and low-density lipoprotein (LDL) cholesterol and low levels of triglycerides, while children treated with carbamazepine had high levels of total cholesterol, triglycerides, LDL and high-density lipoprotein (HDL) cholesterol. Children treated with valproate had low triglycerides and LDL cholesterol levels with high levels of HDL cholesterol. The patients treated with phenobarbital showed a normalization of all parameters after the end of therapy. **CONCLUSIONS:** Anticonvulsant drugs significantly modify serum lipids and lipoproteins in epileptic children. The changes due to phenobarbital seem to be transient.

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## Effects of long-term treatment with antiepileptic drugs on serum lipid levels in children with epilepsy.

Eiris JM, Lojo S, Del Rio MC, Novo I, Bravo M, Pavon P, Castro-Gago M.

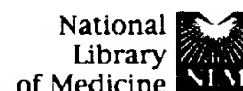
Department of Pediatrics, Hospital General de Galicia, Santiago de Compostela, Spain.

We determined serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), and triglycerides (TGs) in 125 healthy children and in 119 children with epilepsy who had been receiving carbamazepine (58 children), phenobarbital (22 children), or valproic acid (39 children) for 7 months to 10.5 years (mean, 5.8 years). None of the variables considered was significantly correlated with time elapsed since start of treatment or with drug concentration in serum. In the groups receiving carbamazepine or phenobarbital, mean TC, HDL-C, and LDL-C levels were higher than in the control group, the differences being statistically significant for all except LDL-C in the phenobarbital group. In neither group did mean TC/HDL-C ratio or mean LDL-C/HDL-C ratio differ significantly from the corresponding control-group mean. In the group receiving valproic acid, mean TC level, mean LDL-C level, mean TC/HDL-C ratio, and mean LDL-C/HDL-C ratio were significantly lower than in the control group. In none of the treated groups did mean VLDL-C or TG level differ significantly from the corresponding control-group mean. Our results suggest, in contrast to previous reports, that the effects on the serum lipid profile of long-term treatment with hepatic-enzyme-inducing antiepileptic drugs (such as carbamazepine and phenobarbital) are probably not beneficial as regards risk of atherosclerosis-related disease. Our results additionally suggest a need for careful monitoring of serum cholesterol levels in children with epilepsy receiving carbamazepine or phenobarbital.

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GP.  
Total cholesterol, high-density lipoprotein cholesterol, and triglycerides in children receiving  
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Thanks a lot...

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## Changes in serum lipids and lipoproteins in epileptic children treated with anticonvulsants

A VERROTTI<sup>1</sup>, S DOMIZIO<sup>2</sup>, B ANGELOZZI<sup>1</sup>, G SABATINO<sup>2</sup>, G MORGESE<sup>3</sup> and F CHIARELLI

Departments of <sup>1</sup>Pediatrics and <sup>2</sup>Neonatology, University of Chieti, and, <sup>3</sup>Department of Pediatrics, University of Siena, Italy

**Objective:** To assess the effect of long-term treatment of phenobarbital, carbamazepine and sodium valproate on serum lipids and lipoproteins in epileptic children.

**Methodology:** One hundred and fourteen (55 male, 59 female) children and adolescents suffering from various types of epilepsy who received different antiepileptic drugs were studied. The patients were subdivided into three groups according to their therapy: (i) carbamazepine (35 patients); (ii) phenobarbital (34 patients); and (iii) sodium valproate (45 patients). One-hundred healthy sex- and age-matched children served as controls. Lipids and lipoprotein profile were evaluated before the beginning of the anticonvulsant therapy and after at least 2.5 years. In the patients receiving phenobarbital, we re-evaluated 12 children (seven male, five female) at the end of therapy.

**Results:** The children receiving phenobarbital showed high levels of serum total cholesterol and low-density lipoprotein (LDL) cholesterol and low levels of triglycerides, while children treated with carbamazepine had high levels of total cholesterol, triglycerides, LDL and high-density lipoprotein (HDL) cholesterol. Children treated with valproate had low triglycerides and LDL cholesterol levels with high levels of HDL cholesterol. The patients treated with phenobarbital showed a normalization of all parameters after the end of therapy.

**Conclusions:** Anticonvulsant drugs significantly modify serum lipids and lipoproteins in epileptic children. The changes due to phenobarbital seem to be transient.

Many studies, mainly carried out on adult populations, have provided the evidence that there is a significant influence of long-term antiepileptic drugs (AED) therapy on total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and apolipoproteins levels.<sup>1–7</sup> The few studies in the paediatric literature on the effects of the antiepileptic therapy on lipid metabolism are limited in terms of patient numbers and show contradictory results.<sup>8–11</sup> For example, Hendelberg *et al.*<sup>11</sup> found that HDL-cholesterol is very high in children receiving sodium valproate and carbamazepine and that children treated with phenobarbital and sodium valproate showed lower TG levels than controls, while Franzoni *et al.*<sup>8</sup> did not find any significant abnormalities in serum lipids. The patients studied often received a combination of antiepileptic drugs (AED), for different periods of time and there are no prospective studies.

Our study was conducted in order to investigate the possible changes in serum lipids and lipoprotein levels in a large number of epileptic children receiving monotherapy for a long period of time and to investigate the reversibility of the effect of AED on lipids after the end of the therapy.

### METHODS

We studied 114 (55 male, 59 female) children and adolescents suffering from various types of epilepsy who received different

AED. The patients were subdivided into three groups according to their therapy: (i) group A, phenobarbital (34 patients, age range 13.4–18.1 years); (ii) group B, carbamazepine (35 patients, age range 10.0–19.6) and (iii) group C, sodium valproate (45 patients, age range 11.9–18.0). The group A children suffered from generalized tonic-clonic and simple partial seizures, while the large majority of patients of the group B showed complex partial seizures. The patients with tonic-clonic absence and/or minor motor seizures were treated with sodium valproate (group C). Treatment always began with one drug, its dosage being increased until seizures were controlled without developing toxicity. If a second drug was added the patient was excluded from the study. None of the patients had been treated with adrenocorticotrophic hormone (ACTH). Gender and duration of treatment were similar in the three groups.

We evaluated the lipids and lipoprotein profile before anticonvulsant therapy and after at least 2.5 years. In the group of patients receiving phenobarbital, we have been able to re-evaluate 12 children (7 male, 5 female) who stopped their therapy after a period of mean  $1.2 \pm 0.5$  years (range 1.0–1.7 years).

One-hundred healthy sex-matched children with range of age from 10.0 to 19.6 years, served as controls. The control group had never received any AED or other drugs that can affect lipids and lipoprotein metabolism and had never suffered from endocrinological, metabolic or renal disease. None of the subjects followed dietary restriction. The patients and the controls lived in the same area with the same dietary habits. The patients studied did not change significantly their physical exercise and dietary habits during the study. There was no difference in physical activity and diet between the epileptic patients and the controls.

The diet of the children studied (patients and controls) was

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analysed by a questionnaire: each patient was interviewed and invited to fill out a questionnaire concerning the kind and amount of food consumed every day in the week preceding the interview. Both patients and controls estimated the size and the amount of food eaten by units of weight, volume or household measure or with the aid of graduated food models. Data on home food and food preparation were also collected from the parents by a questionnaire.

All plasma levels of AED were within the therapeutic range: carbamazepine  $7.0 \pm 1.9 \mu\text{g/mL}$ , sodium valproate  $62.4 \pm 19.4 \mu\text{g/mL}$ , phenobarbital  $17.5 \pm 2.7 \mu\text{g/mL}$ . All blood samples were drawn fasting in the morning and before the first day drug-dose. Lipids were measured in serum and the HDL containing supernatant after precipitation of apo B containing lipoproteins. Cholesterol and triglycerides were measured enzymatically, as previously described<sup>12</sup> using automated methods. Low-density lipoprotein cholesterol was calculated by the Friedewald formula.

High-density lipoprotein was isolated by ultracentrifugation.<sup>13,14</sup> The background density of plasma was adjusted to  $1063 \text{ gL}^{-1}$  by adding a sodium chloride-potassium bromide solution. The infranats were obtained by tube slicing after ultracentrifugation at  $100\,000 \times g$  for 48 h (L8M55 ultracentrifugation with 50.3 Ti Rotor; Beckman, Richmond, VA, USA).<sup>15</sup>

In view of the possibility that lipoprotein (a) might interfere with the isolation of HDL by ultracentrifugation, HDL was also isolated by precipitation of other lipoproteins, including lipoprotein (a), with sodium phosphotungstate and magnesium chloride.<sup>16,17</sup> Total serum apolipoprotein A1 and B concentrations were determined by immunoelectrophoresis using goat-antisera (Immuno, Duntun Green, Kent, UK). The within-batch coefficient of variation of the assay was 5.4%.

Serum lipoprotein (a) concentrations were measured, using a two-site radioimmunoassay (Pharmacia Diagnostics, Sweden). After hydrolysis and dilution, the serum sample was incubated with an excess of  $^{125}\text{I}$ -labelled anti-apo (a) monoclonal antibody and a different monoclonal antibody coupled to micro-sepharose. Antibody-antigen complexes were separated from unbound  $^{125}\text{I}$  by centrifugation and their radioactivity was measured. A standard curve was constructed for each assay. The within-assay coefficient of variation was 6%. Results are expressed in terms of the Pharmacia standard and are in U/dL.

### Statistical methods

Results are expressed as mean  $\pm$  SD or medians and ranges for data not normally distributed; *P* values less than 0.05 were considered significant. All variables measured have been checked for normality and adjusted using Duncan's method, as appropriate. The comparison of data among groups was performed by Wilcoxon's rank sum test and by paired and unpaired Student's *t*-test. Moreover, Spearman's rank correlation coefficient was performed.

### RESULTS

The mean serum levels of lipids and lipoproteins of the three groups of patients and controls before the beginning of the therapy and during treatment are given in Table 1. Before the treatment, all the children showed similar values to those of the control group. The data of the patients after at least 2.5 years of treatment are shown in Table 1.

The children receiving phenobarbital showed high levels of serum TC and LDL cholesterol and low levels of TG, while group B children had high levels of TC, TG, LDL and HDL cholesterol; finally, children treated with valproate (group C) had low TG and LDL cholesterol levels with high levels of HDL cholesterol.

There was no significant difference in the levels of serum apolipoproteins A1 and B between the three groups of patients and controls. In epileptic patients, no significant correlation was found between AED plasma concentrations and lipids and lipoproteins levels.

There was no difference in growth between the groups of patients. All subjects showed a body mass index between 10th to 90th percentile. In order to evaluate liver function, serum transaminases and alkaline phosphatase concentrations were assessed: all patients showed normal values.

The values of lipids and lipoproteins of children who discontinued phenobarbital were compared with the values during treatment. After the end of therapy, all the values were similar to those observed before beginning therapy.

### DISCUSSION

Our study shows that even in children and adolescents receiving AED it is possible to find significant abnormalities in the serum lipids and lipoprotein profile. These data are in agreement with previous studies performed in adult epileptic patients.<sup>1-7</sup> In fact, Nikkila *et al.*<sup>1</sup> reported an increase in HDL cholesterol and TG levels, and Berlitz *et al.*<sup>3</sup> found a significant increase of all lipid fractions in adult patients receiving various AED, while others<sup>2,10</sup> reported high TC levels in patients treated with phenytoin. Patient groups were not always clearly defined and very often they received AED polytherapy. In the present study all the epileptic children were treated with monotherapy for at least 2.5 years. Consequently, it has been possible to evaluate the effect of the single AED on the lipid parameters after a long period of time.

The baseline lipids and lipoproteins serum levels in our children indicate that changes in concentration do not result from the convulsive disorder itself, but are the consequence of the AED administration, although no significant correlation was found between AED plasma concentrations and serum lipids and lipoproteins levels.

We found a significant increase of TC and LDL cholesterol in children in treatment with phenobarbital. This is in contrast to previous studies<sup>8,9</sup> but, in agreement with others.<sup>3,11</sup> It is possible that phenobarbital, as with other drugs that may cause hypertrophy of liver microsomes, can induce a proliferation of the endoplasmic reticulum, which is probably the site in liver cells where the lipoprotein lipids are synthesized and organized to particles. This reticulum can be the main subcellular structure stimulated by phenobarbital with consequent changes in lipoproteins levels. This hypothesis is supported by some biochemical studies<sup>18-21</sup> which demonstrated that barbiturates cause a marked increase in the enzymes, protein and lipid content of the hepatic smooth endoplasmic reticulum and can modify many microsomal and mitochondrial enzymes.

Children treated with carbamazepine showed high levels of TC, TG and HDL cholesterol; these data are in agreement with those reported by Isojarvi *et al.*<sup>5</sup> who demonstrated this in adult patients. Other authors<sup>4,6,10,11</sup> found these abnormalities in patients treated with carbamazepine, while others did not

Table 1 Serum lipids of the three groups of patients (before and during treatment) and in controls

	Controls	Phenobarbital	Carbamazepine	Sodium valproate	Phenobarbital	Carbamazepine	Sodium valproate
Number of patients (M/F)	100 (50/50)	34 (16/18)	35 (17/18)	45 (22/23)	34 (16/18)	35 (17/18)	45 (22/23)
Age (years)	15.6 ± 5.9	15.7 ± 2.4	15.2 ± 5.2	14.7 ± 3.3	20.6 ± 2.7	19.8 ± 5.2	19.8 ± 5.9
Dosage (mg/kg)					3.2 ± 0.5	16.7 ± 8.2	52.7 ± 12.9
Duration of treatment (year)					3.9 ± 0.7	2.5 ± 2.7	3.1 ± 2.9
Serum cholesterol (mmol/L)	4.46 ± 0.92	4.47 ± 0.73	4.45 ± 0.81	4.48 ± 0.67	5.6 ± 1.11	5.71 ± 1.521	4.67 ± 1.14
Serum triglycerides (mmol/L)	1.21 ± 0.42	1.23 ± 0.21	1.2 ± 0.5	1.22 ± 0.31	1.01 ± 0.30	1.49 ± 0.62	1.02 ± 0.67
LDL cholesterol (mmol/L)	2.31 ± 0.50	2.32 ± 0.61	2.33 ± 0.32	2.3 ± 0.4	2.56 ± 0.61	2.61 ± 0.54	2.05 ± 0.83
VLDL (mmol/L)	0.52 ± 0.21	0.51 ± 0.32	0.5 ± 0.40	0.53 ± 0.10	0.55 ± 0.81	0.53 ± 0.86	0.56 ± 0.45
HDL (mmol/L)	1.31 ± 0.46	1.32 ± 0.30	1.33 ± 0.21	1.34 ± 0.14	1.42 ± 0.32	2.01 ± 0.601	1.94 ± 0.521
Apolipoprotein A1 (mmol L <sup>-1</sup> )	4.9 10 <sup>-2</sup> ± 2 10 <sup>-3</sup>	5.1 10 <sup>-2</sup> ± 2 10 <sup>-3</sup>	4.8 10 <sup>-2</sup> ± 2 10 <sup>-3</sup>	5.0 10 <sup>-2</sup> ± 2 10 <sup>-3</sup>	4.7 10 <sup>-2</sup> ± 12 10 <sup>-3</sup>	5.0 10 <sup>-2</sup> ± 2 10 <sup>-3</sup>	4.7 10 <sup>-2</sup> ± 12 10 <sup>-3</sup>
Apolipoprotein B (mmol L <sup>-1</sup> )	1.9 10 <sup>-3</sup> ± 1.3 10 <sup>-4</sup>	1.8 10 <sup>-3</sup> ± 1.2 10 <sup>-4</sup>	1.7 10 <sup>-3</sup> ± 1.4 10 <sup>-4</sup>	1.85 10 <sup>-3</sup> ± 1.25 10 <sup>-4</sup>	1.7 10 <sup>-3</sup> ± 1.3 10 <sup>-4</sup>	1.7 10 <sup>-3</sup> ± 1.3 10 <sup>-4</sup>	1.7 10 <sup>-3</sup> ± 1.3 10 <sup>-4</sup>
Apo (a)	81.3 (16-790)	87.8 (12-776)	89.1 (14-781)	83.1 (14-910)	80.1 (18-904)	84.1 (18-902)	81.4 (16-915)

\*P < 0.05 patients vs controls; †P < 0.01 patients vs controls; M, male; F, female; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein.

confirm these findings.<sup>8</sup> It is possible that these changes can be due to an increase in gamma-glutamyltransferase activity, sometimes reported elevated in patients treated with this AED.<sup>9</sup> In our study, we evaluated only transaminases and alkaline phosphatase.

Patients treated with sodium valproate showed a decrease of TG and LDL cholesterol, with an increase of HDL. It is possible that biochemical hepatic injury, demonstrated recently,<sup>20,22</sup> can be the cause of these changes. Our data are in agreement with those of Heldenberg<sup>11</sup> but not with those of Zeithofer<sup>8</sup> who found a significant decrease in apolipoprotein A1 and in apolipoprotein B. This latter study was of adults with a short duration of treatment (6 months). In another study<sup>8</sup> TC levels were significantly increased by carbamazepine and phenobarbital, while valproate showed a mild but significant decrease in comparison to the levels of controls.

The differences between our results and those of others can be explained by the different ages of population studied, prospective vs retrospective analysis, one or more antiepileptic drugs received and different follow-up periods. In particular, frequently, only adult patients have been studied,<sup>3-6</sup> in another study,<sup>8</sup> performed on paediatric patients, the authors described the mean values of plasma lipids in children receiving antiepileptic drugs of any kind. Moreover, many previous studies<sup>1-3,5,6,8,9,11</sup> did not study the changes of apolipoproteins which have been analysed in our research. Finally, to best of our knowledge, this is the first paper reporting a study of lipids and lipoproteins in a significant number of patients receiving a single drug. We found that all the AED studied can interfere with lipid metabolism in monotherapy.

Finally, we have had the opportunity to re-evaluate a small group of patients receiving phenobarbital after the discontinuation of their therapy. All patients showed a complete normalization of the abnormalities found during therapy; our study suggests that the changes observed during the therapy are transient, and that they reverse after the end of the therapy without any permanent modification of lipid metabolism.

In conclusion, this study confirms that carbamazepine, phenobarbital and sodium valproate can modify the serum lipids and lipoprotein levels in a long term treatment on a paediatric population.

Although these changes of lipids and lipoproteins seem to be mild, it is not clear if these changes can increase the risk of atherosclerosis; an epidemiological study, performed on a large group of patients receiving antiepileptic drugs could be useful to solve this question. Antiepileptic drugs should be added to the list of drugs that may affect lipid concentration and we suggest that children who receive these drugs should be advised to follow a normocaloric diet, with a low percentage of saturated lipids.

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